NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA323; Erythropoiesis-stimulating agents (epoetin and darbepoetin) for the treatment of cancer-treatment induced anaemia

Original publication date:	November 2014
Review date	November 2017
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA323, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Rationale

There has been no substantial change in the wordings of the marketing authorisation of the technologies, recommended in the technology appraisal guidance 323, concerning chemotherapy-induced anaemia. Some biosimilars have received European marketing authorisation since the publication of TA323 for example Abseamed and Epoetin Alfa Hexal (epoetin alfa), Biopoin (epoetin theta) and Silapo (epoetin zeta). However these products are currently not available in the UK. Teva UK has confirmed that they are no longer marketing Eportio (epoetin theta), one of the recommended options in TA323, in the UK. The list prices for the recommended technologies have not substantially changed since the publication of TA323 in November 2014.

The evidence review during the development of TA323 established that erythropoiesis-stimulating agents were effective in increasing haemoglobin concentrations, improving haematological responses thereby reducing the need for blood transfusions and improving health-related quality of life. The main concerns were their effect on overall survival, tumour growth, and adverse reactions particularly high risk of thromboembolism.

Studies published since the searches were last run during the development of TA323 (December 2013), reconfirm the earlier conclusion. Owing to the potential negative effect on survival, tumour progression, the use of erythropoiesis-stimulating

agents has gone out of favour as a standalone treatment of chemotherapy-induced anaemia (Weigl et al, 2017).

As the regulatory agencies in Europe have not issued any new safety warning, it is expected that clinicians will adhere to the instructions stipulated in the section 4.4 ‘Special warnings and precautions for use’ in respective summaries of the product characteristics regarding starting, stopping and, dose adjustments taking into account haemoglobin level, to mitigate the risk of harm.

As there is no evidence which could have an impact on the previous recommendations, it is recommended to move the guidance on the static list.

3. Summary of new evidence and implications for review

Randomised trials:
An open-label, post-marketing study (Leyland-Jones et al., 2016) evaluated the impact of epoetin alfa on tumour progression in people with metastatic breast cancer receiving chemotherapy) who also had anaemia (n=2,098). The randomised study was designed to demonstrate non-inferiority of epoetin alfa on progression-free survival compared with standard treatment. The study was not able to rule out increased risk of tumour progression or death with epoetin alfa. Thromboembolic events were statistically significantly more frequent with epoetin alfa (2.8%) than with best supportive care group (1.4%), P value=0.038. Transfusion rates were significantly lower with epoetin alfa (5.8%) than with best supportive care group (11.4%), P value<0.001, however the authors concluded blood transfusion as a preferred treatment option for treating anaemia in people with metastatic breast cancer receiving chemotherapy.

A conference abstract (Mackelenbergh et al., 2017) reported a sub-analysis of German adjuvant intergroup node-positive study (GAIN). GAIN is a randomised trial which compared two dense chemotherapy regimen in women with breast cancer that has spread to axillary lymph nodes. All patients received either primary prophylaxis with epoetin beta (450unit/kg weekly) or darbepoetin alfa (D) (4.5µg/kg biweekly). The sub-analysis reported comparable rate of anaemia and thromboembolic events, disease free survival and overall survival in women receiving either epoetin beta or darbepoetin alfa.

Mountzios et al. (2016) reported long-term safety and survival outcomes of a prematurely terminated randomized controlled trial that compared prophylactic with haemoglobin-based administration of erythropoiesis-stimulating agents in patients with chemotherapy-induced anaemia. There was no significant differences in disease or progression-free and overall survival with respect to prophylactic or hameoglobin-based administration groups. The patients in the prophylactic group benefitted by lower incidence of anaemia and fatigue but had a marginally higher rate of thrombosis-related adverse events.

Nitz et al., (2014) reported results from a randomised trial that evaluated the effect of darbepoetin alfa in people with node positive breast cancer receiving adjuvant chemotherapy after surgery. Incidence of venous thromboembolism were statistically significantly higher in people receiving darbepoetin alfa, whereas other outcomes

such as event free survival, overall survival, quality of life measure (FACT-An, or FACT-Cog) did not differ significantly.

A randomized, open-label study compared the effect of adding epoetin alfa in people with inoperable, stage III non-small cell lung cancer having sequential radio-chemotherapy (Debus et al., 2014). At 2 year, overall survival was not significantly different between 2 groups. In people who received epoetin alfa along with sequential radio-chemotherapy, transfusion rates were lower (12.3 vs. 32.1%) and thromboembolic events were higher (16.7% vs. 7.9%) compared with people who received sequential radio-chemotherapy alone.

Systematic Reviews:

Searches identified a number of systematic reviews that used study-level meta-analysis to synthesise evidence. Most of the studies included in these meta-analyses were included or considered for inclusion by the Assessment Group during the development of TA323.

These meta-analyses are listed below,

- Aapro et al. (2015) included 9 RCTs in people with breast cancer
- Marchetti et al. (2016) included 7 RCTs in people with gynaecological cancers
- Forbes et al. (2014) included 14 RCTs and 11 observational studies in people with solid tumours.
- Bohlius et al. (2014) included 37 RCTs reporting quality of life measures in people with solid, haematological or solid and haematological cancers.

Broadly the conclusion of the reviews was consistent with the committee's conclusion that ESAs are associated with improvement in anaemia related symptoms, less requirement of blood transfusion, higher incidence of thromboembolic events and statistically non-significant higher mortality or progression.

A patient-level meta-analysis by Pirker et al. (2016), explored effectiveness of darbepoetin alfa when initiated at a haemoglobin level of 10 gm/dL or less. This analyses included data from industry-sponsored; 4 comparative studies and 15 non-comparative studies. The author concluded that darbepoetin alfa is effective at rapidly increasing haemoglobin level and reducing the need for transfusions in patients with chemotherapy-induced anaemia when initiated after haemoglobin level less than10 g/dL, as per current licence.

Has there been any change to the price of the technologies) since the guidance was published?
No
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

No
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
Yes
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
N/A

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from May 2013 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

N/A.

GE paper sign off: Meindert Boysen, 8 November 2017

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) within their licensed indications for the treatment of cancer-treatment induced anaemia.

6. Current guidance

1. Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

2. If different erythropoiesis‑stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.

7. Research recommendations from original guidance

Not applicable.

8. Cost information from original guidance

To cost the erythropoiesis stimulating agents, the Assessment Group used the list price per 1000 units from the British national formulary (BNF, March 2014) for Eprex (£5.53), Binocrit (£5.09), NeoRecormon (£7.01), Eporatio (£5.99) and Retacrit (£5.66), and per microgram for Aranesp (£1.47).

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the specify STA or MTA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to specify date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

None

2. Details of changes to the indications of the technologies

Indication and price[2] considered in original appraisal	Proposed indication (for this appraisal) and current price[3]
Epoetin alfa *Eprex brand* *"treatment of anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, who are at risk of transfusion as assessed by the patient's general status (for example, cardiovascular status, pre-existing anaemia at the start of chemotherapy)"* Price: £5.53 per 1000 units *Binocrit brand* Binocrit is a biosimilar medicine referenced to Eprex and shared the same UK marketing authorisation wording. Price: £4.33 per 1000 units	*Eprex brand* The indication considered in the original TA is still current. Price: no change *Binocrit brand* No change to original licensed indication. Price: Not listed on either C+D data or BNF [online], 18th September 2017.
Epoetin beta *NeoRecormon brand*	*NeoRecormon brand*

[2] Prices are excluding VAT and were originally taken from the British national formulary [BNF], March 2014

[3] Excluding VAT, taken from C+D data [online], accessed 18th September 2017.

Indication and price[2] considered in original appraisal	**Proposed indication (for this appraisal) and current price[3]**
"treatment of symptomatic anaemia in adult patients with non-myeloid malignancies who are receiving chemotherapy" Price: £3.51 per 500 units	No change to licensed indication. Price: no change
Epoetin theta *Eporatio brand* "treatment of symptomatic anaemia in adult patients with non-myeloid malignancies who are receiving chemotherapy" Price: £5.99 per 1000 units	*Eporatio brand* No change to licensed indication. Price: no change
Epoetin zeta *Retacrit brand* Retacrit is a biosimilar medicine referenced to Eprex and shared the same UK marketing authorisation wording Price: £5.66 per 1000 units	No change to original licensed indication. Price: £4.81 per 1000 units
Darbepoetin alfa *Aranesp brand* "treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies who are receiving chemotherapy". Price: £14.68 per 10 micrograms	*Aranesp brand* No change to licensed indication. Price: £14.68 per 10 micrograms

3. Registered and unpublished trials

Appendix C

Trial name and registration number	Details
A randomized, double-blind, placebo-controlled study to evaluate the long-term safety and efficacy of darbepoetin alfa administered at 500 µg once-every-3-weeks in anemic subjects with advanced stage non-small cell lung cancer receiving multi-cycle chemotherapy NCT00858364; 20070782	Darbepoetin vs. placebo n = 2549 Study completed 7th June 2017. Terminated early: *"primary objective reached"*.
A randomized, open-label, multicenter, phase 3 study of epoetin alfa plus standard supportive care versus standard supportive care in anemic patients with metastatic breast cancer receiving standard chemotherapy NCT00338286; CR005143; EPOANE3010; CR005143; 2005-001817-17	n = 2098 Data collection for the primary outcome was completed in 2014 and reported at clinicaltrials.gov. Estimated overall study completion date: June 2019.

Appendix D – References

Weigl A, Köhler N, Monsef I, et al. (2017) Intravenous iron versus oral iron versus no iron with or without erythropoiesis- stimulating agents (ESA) for cancer patients with anaemia: A systematic review and network meta-analysis *Cochrane Database of Systematic Reviews* (4).

Leyland-Jones B, Bondarenko I, Nemsadze G, et al. (2016) A Randomized, Open-Label, Multicenter, Phase III Study of Epoetin Alfa Versus Best Standard of Care in Anemic Patients With Metastatic Breast Cancer Receiving Standard Chemotherapy *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 34 (11): 1197-207.

Mackelenbergh M, Loibl S, Jackisch C, et al. (2017) Efficacy and safety of darbepoetin alfa or epoetin beta in 2994 high risk early breast cancer patients participating in the German adjuvant intergroup node-positive study (GAIN) Cancer research. *Conference: 39th annual CTRC-AACR San Antonio breast cancer symposium. United States* 77 (4 Supplement 1)

Mountzios G, Aravantinos G, Alexopoulou Z, et al. (2016) Lessons from the past: Long-term safety and survival outcomes of a prematurely terminated randomized controlled trial on prophylactic vs. hemoglobin-based administration of erythropoiesis-stimulating agents in patients with chemotherapy-induced anemia *Molecular and Clinical Oncology* 4 (2): 211-20.

Nitz U, Gluz O, Zuna I, et al. (2014) Final results from the prospective phase III WSG-ARA trial: impact of adjuvant darbepoetin alfa on event-free survival in early breast cancer *Annals of oncology : official journal of the European Society for Medical Oncology* 25 (1): 75-80.

Debus J, Drings P, Baurecht W, et al. (2014) Prospective, randomized, controlled, and open study in primarily inoperable, stage III non-small cell lung cancer (NSCLC) patients given sequential radiochemotherapy with or without epoetin alfa Radiotherapy and oncology : *Journal of the European Society for Therapeutic Radiology and Oncology* 112 (1): 23-9

Aapro M, Moebus V, Nitz U, et al. (2015) Safety and efficacy outcomes with erythropoiesis-stimulating agents in patients with breast cancer: a meta-analysis *Annals of oncology : official journal of the European Society for Medical Oncology* 26 (4): 688-95.

Marchetti C, De F, Palaia I, et al. (2016) Erythropoiesis-stimulating agents in gynecological malignancies: A study-level meta-analysis *Critical reviews in oncology/hematology* 99: 123-8.

Forbes Carol A, Worthy G, Harker J, et al. (2014) Dose efficiency of erythropoiesis-stimulating agents for the treatment of patients with chemotherapy-induced anemia: a systematic review *Clinical therapeutics* 36 (4): 594-610.

Bohlius J, Tonia T, Nuesch E, et al. (2014) Effects of erythropoiesis-stimulating agents on fatigue- and anaemia-related symptoms in cancer patients: systematic review and meta-analyses of published and unpublished data (Provisional abstract) *Database of Abstracts of Reviews of Effects* (2): 33-45.

Pirker R, Hedenus M, Vansteenkiste J, et al. (2016) Effectiveness of Darbepoetin Alfa for Chemotherapy-induced Anemia When Initiated at Hemoglobin <10 g/dL *Clinical therapeutics* 38 (1): 122e6-135e6.